UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,776	01/25/2002	Kurt Berlin	81796	9632

7590 10/15/2003

KRIEGSMAN & KRIEGSMAN
665 Franklin Street
Framingham, MA 01702

EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 10/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,776	BERLIN, KURT	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-13 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) 6 is/are allowed.

6)☒ Claim(s) 1-13 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Compliance Notice* .

DETAILED ACTION

Priority

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Drawings

There are no drawings in the application.

Specification

This application contains sequence disclosures that are encompassed by the definition for nucleotide and/or amino acid sequences set for in 37 CFR 1.82(a)(1) and (a)(2). However, this application fails to comply with the requirement of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotides Sequences And/Or Amino Acid Sequence Disclosures. For example, from page 15-18, the specification discloses nucleotide sequences which are not defined by their SEQ ID Numbers.

Applicants are advised that a fully responsive communication **MUST** comply with the Sequence Requirements.

Claim Objections

Claim 6 is objected to because of the following informalities: claim 6 recites that a "bisulfate solution" is used as a reagent. However, this appears to be a typographical error since

the instant specification, on page 9, 2nd paragraph, discloses that the method is conducted with "bisulfite solution." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite for the recitation of the phrase, "whereby the immobilized oligomers hybridize at least to one of the primers ***or their complementary sequences used in the amplification step***," because it is not clear whether the recited complementary sequence is referring to the genomic DNA sequences or other nucleic acid sequences. For the purpose of prosecution, the complementary sequence is assumed to be the genomic DNA sample.

Claim 10 recites the limitation "the primers" and "the hybridizing" in step (b) and (c), respectively. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3, 6, 7, 10, and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by Gonzalgo et al. (WO 98/56952, published December 17, 1998).

Gonzalgo et al. disclose a method of fluorescently detecting the methylated cytosine in a genomic DNA sample (claim limitation 1), wherein the genomic DNA is first treated with a bisulfite (page 4, line 15; claim limitation 6), the DNA amplified by PCR or polymerase chain reaction (page 7-8; claim limitation 7), amplicons separated via electrophoresis (page 5, line 24; claim limitation 3), and the amplicons detected radioactively (page 4, lines 10-30) or fluorescently (page 8, lines 30-31; claim limitation 12). Gonzolago et al. also disclose a method of detecting the methylated cytosine, wherein the amplicons are transferred onto a nylon membrane for dot-blot analysis (page 8, lines 34-35; claim limitation 2 and 10).

Therefore, Gonzalgo et al. anticipate the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8, 9, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al. (WO 98/56952, published December 17, 1998) in view of Yurov et al. (Human Genetics, 1996, vol. 97, pages 390-398).

Claims are drawn to a method of quantitating the methylation of cytosine bases in a DNA sample which comprises treating the DNA with a reagent, wherein the reagent is a bisulfite,

amplifying the treated DNA, and detecting the amplified products via differentially labeled fluorescent dNTPs, wherein the labels are cy3 and cy5.

Gonzalgo et al. disclose a method of fluorescently detecting the methylated cytosine in a genomic DNA sample, wherein the genomic DNA is first treated with a bisulfite (page 4, line 15), the DNA amplified by PCR or polymerase chain reaction (page 7-8), amplicons separated via electrophoresis (page 5, line 24), and the amplicons detected radioactively (page 4, lines 10-30) or fluorescently (page 8, lines 30-31). Gonzalgo et al. also disclose a method of detecting the methylated cytosine, wherein the amplicons are transferred onto a nylon membrane for dot-blot analysis (page 8, lines 34-35).

The method disclosed by Gonzalgo et al. do not employ the differentially labeled fluorescent NTPs comprising cy3 and cy5.

Yurov et al. disclose the use of multicolor fluorescence detection via use of cyanine dyes, more specifically, cy3 and cy4 (page 391, 1st column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Gonzalgo et al. with the teachings and suggestions of Yurov et al. to arrive at the invention as claimed for the following reasons.

Although Gonzalgo et al. do not explicitly recite that cy3 and cy5 be used as fluorescent labels, Gonzalgo et al. do suggest that their method is achieved via use of fluorescent labels:

"There are several techniques that are able to determine the relative amount of methylation at each CpG site, for example... or even using fluorescent probes instead of a ^{12}P marker" (page 8, lines 30-31).

In addition to this suggestion, Yurov et al. disclose an explicit benefit of using the cy3 and cy5 dye over the traditional fluorescent labels:

"Cyanine dyes are also useful as fluorescent labels or biological macromolecules. Cyanine 3 dye provides significantly ***brighter*** fluorescence than any other fluorophore, including fluorescein..." (page 391, 1st column).

Yurov et al. also disclose the advantage of using cy3 and cy5 dyes for multicolor detection (page 391, 2nd column).

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to take the suggestion of Gonzalgo et al., that is, the feasibility of using fluorescent markers for the detection, with the explicit advantage disclosed by Yurov et al. with a reasonable expectation of success because by doing so, one of ordinary skill in the art would have been able to realize the advantages the cyanine dyes had to offer (i.e., multicolor detection, brighter dyes).

Therefore, the invention as claimed is obvious over the cited references.

Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al. (WO 98/56952, published December 17, 1998) in view of Apffel et al. (U.S. Patent No. 6,379,889 B1, issued April 30, 2002, filed November 4, 1999) and Roche et al. (Biotechnology Progress, 1997, vol. 13, pages 659-668).

Claims are drawn to a method of quantitating the methylation of cytosine bases in a DNA sample wherein the separation of the PCR products is achieved by either High Performance Liquid Chromatography (HPLC) or Capillary Gel Electrophoresis (CGE).

Gonzalgo et al. disclose a method of fluorescently detecting the methylated cytosine in a genomic DNA sample, wherein the genomic DNA is first treated with a bisulfite (page 4, line 15), the DNA amplified by PCR or polymerase chain reaction (page 7-8), amplicons separated via conventional electrophoresis (page 5, line 24), and the amplicons detected radioactively (page 4, lines 10-30) or fluorescently (page 8, lines 30-31). Gonzalgo et al. also disclose a method of detecting the methylated cytosine, wherein the amplicons are transferred onto a nylon membrane for dot-blot analysis (page 8, lines 34-35).

The method disclosed by Gonzalgo et al. do not explicitly disclose the use of HPLC or CGE for PCR product separation.

Apffel et al. disclose a method of using HPLC for the separation of PCR amplicons from a PCR reaction mixture (column 3, lines 45-48)

Roche et al. disclose a method of using GCE for the separation of PCR amplicons (pp. 663, 2nd column bottom).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to expand the teachings of Gonzalgo et al. with the teachings of Apffel et al. and Roche et al. to arrive at the invention as claimed per suggestion offered by Gonzalgo et al., wherein the artisans state:

"There are many chromatographic techniques that can be used to isolate PCR amplification products (*or amplicons*)" (pp. 8, line 7-9).

One of ordinary skill in the art at the time the invention was made would have recognized various chromatographic techniques for separation/purification and the advantage offered by such techniques, as illustrated by Apffel et al. and Roche et al.:

"CE is capable of rapid, automated, reproducible, and high-resolution separation of small volumes of complex mixtures." (pp. 659, 2nd column; pp. 664, 1st column, *Roche*).

"Distinguish individual PCR amplicons (also referred to as PCR products herein) from a PCR reaction mixture." (column 3, lines 44-47).

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to modify the teaching of Gonzalgo et al. given their explicit statement of feasibility to realize the advantages offered by the separation techniques of Apffel et al. and Roche et al. with a reasonable expectation of success.

Therefore, the invention as claimed is obvious over the cited references.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al. (WO 98/56952, published December 17, 1998) in view of Wang et al. (Science, May 1998, vol. 280, pages 1077-1082).

The teachings of Gonzalgo et al. has been set forth above.

Gonzalgo et al. do not explicitly disclose that the amplification was multiplexed.

Wang et al. disclose a mehtod of SNP genotyping which involves multiplex amplification from a genomic DNA via plurality of primers (pp. 1080). Wang et al. multiplexes 46 loci from a genomic DNA (pp. 1080, 3rd column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Gonzalgo et al. with the teachings and advantages disclosed by Wang et al. to arrive at the invention as claimed for the following reason.

Wang et al. clearly suggest the well-known advantage of multiplexing PCR reactions:

"We next sought to ***decrease substantially the sample preparation*** required to genotype large numbers of SNPs, as required to perform a genomic scan. We developed a protocol based on multiplex PCR in which primer pairs from many different loci are combined in a single reaction." (page 1080, 3rd column).

One of ordinary skill in the art, therefore, would have been motivated to employ the well-known multiplex-PCR technique into the method disclosed by Gonzalgo et al. for the well-known advantage of reducing the sample preparation/contamination with a reasonable expectation of success.

Therefore, the invention as claimed is obvious over the cited references.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (703) 308-9348. The Examiner can normally be reached from 8:30 a.m. to 7:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (703)-308-3905. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (703) 308-1119. Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (703) 872-9306. For Unofficial documents, faxes can be sent directly to the Examiner at (703) 746-3172. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Young J. Kim

10/7/03

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

10/9/03